REMARKS

With entry of the instant amendment, claims 3, 4, 19, 30, and 32 have been amended and claims 2, 6, and 14-18 have been cancelled. Claims 7-13, 25, 27-29, 31, and 38-42 were previous cancelled; claims 34 and 35 are withdrawn. Thus, claims 1, 3, 4, 5, 19-24, 26, 30, 32, 33, 36, and 37 are currently under examination.

The amendments to the claims add no new matter and are supported throughout the application as filed.

Claim 3 has been amended to recite that the sequence comprises the coding region of SEQ ID NO:1. Support can be found, *e.g.,* in Figure 1.

Claim 30 has been amended to recite that the transfected cell is *in vitro*. Support can be found, *e.g.,* on page 25 and page 29, lines 6-7.

For convenience, the objections/rejections will be addressed in the order presented in the Office Action dated May 18, 2004.

Objection to the specification

The Examiner has maintained the objection to the specification with regard to Applicants' correction of a typographical error. The Examiner maintains that U.S. Patent No. 6,107,462 "establishes" that the hybridization conditions reciting formalin with 1 mg of heparin were known and used in the art and that one of skill would not readily recognize that the error is an obvious error. Applicants respectfully disagree. The Examiner has only produced one patent that recites formalin with 1 mg of heparin in a hybridization reaction. Applicants have identified multiple manuals routinely used in the art, none of which refer to hybridization using formalin with 1 mg of heparin, but do disclose hybridization reaction employing formamide. The Examiner has not established that one of skill would not reasonably understand that the "formalin" hybridization reaction is an obvious error. However, in order to expedite prosecution, Applicants have cancelled the previous amendment to the specification.

Maintained rejections under 35 USC § 112, first paragraph

Claims 1-3, 4, 5, 6, 30, 32, 33, 36, and 37 are rejected for reasons previously set forth in the paper mailed March 25, 2003, section 4, page 2, drawn to claims 1-3, 5, 30, 32, 33, and 36-37. The rejection at section 4, page 2, refers to the rejection as set forth in paper no. 17, section 6, pages 3-6. At that section in paper number 17, the rejection states that the claims are rejected for the reasons set forth in paper number 13, section 6, pages 5-10. Applicants note that this appears to be referring to paper number 15, not paper number 13, as paper number 13 is not an Office Action on the merits. At section 6, pages 5-10 of paper number 15, the Patent Office acknowledges that the claims are enabled for a polynucleotide encoding the protein of SEQ ID NO:2, or a polynucleotide comprising SEQ ID NO:1 or SEQ ID NO:3. Thus, this rejection does not appear to relate to current claims 3-5.

The Examiner reiterates the position that one of skill in the art would not be able to identity menin proteins with 95% identity to SEQ ID NO:2 and even, if they could, they would not know how to use them. Applicants traverse for reasons of record. Applicants have provided ample guidance that taken with the knowledge in the art, provide sufficient instruction for the artisan to identify the claimed sequences. For example, Applicants teach how to identify such menin proteins using alignment programs. Applicants further, teach regions of the protein that are mutated in disease (*see, e.g.,* Example 1, Figure 3, and Figure 4). The Examiner provides no evidence or reasoning as to why one of skill in the art would not be able to use such sequences, *e.g.*, to raise antibodies to identify wildtype or mutant menin proteins (*see, e.g.,* the specification at page 5, lines 28-30). Applicants therefore respectfully request withdrawal of the rejection.

Claims 1-3, 4, 5, 6, 19, 24, 26, 30, 32, 33, 36, and 37 also stand rejected for the reasons previously set forth in the paper mailed March 25, 2003, Section 5, pages 2-3. The Examiner argues that the Chandrasekharappa Declaration, which provides evidence of the association between the claimed nucleic acids and expressed protein sequences, does not provide a nexus between the sequences of the instant application and those in the references discussed in the Declaration. Applicants traverse.

Dr. Chandrasekharappa is an inventor on this application and an author of Guru *et al.*, which was cited in the Chandrasekharappa Declaration He explicitly states in his Declaration that the Guru *et al.* menin polypeptide and nucleic acid sequences are the same as those the instant application. This statement establishes a nexus. The Examiner has provided no evidence or reasoning as to why one of skill in the art would NOT believe that Dr. Chandrasekharappa would know that these sequences were in fact the same. Therefore, the Examiner does not establish a proper basis for the position that the claims are not enabled. However, in order to expedite prosecution, Applicants provide in Appendix A an alignment of the full-length menin cDNA referred to in Guru *et al.* (top of column 2, page 1630, citing the *Science* Chandrasekharappa *et al.* reference, which was provided as Exhibit C of the Chandrasekharappa Declaration). Chandrasekharappa *et al.* indicate that the GenBank accession number for the cDNA is U93236. Appendix A includes the entry for this accession number in the database (which shows both the cDNA sequence and the translation product) and an alignment of this sequence to SEQ ID NO:1. The alignment confirms that the two sequences are indeed identical.

Wautot *et al.*, provided in Applicants' response mailed January 10, 2003, references Guru *et al.*, the Chandrasekharappa *et al* 1997 *Science* paper, and a paper by the European Consortium 1997 (which is Lemmens *et al*, *Hum Mol Genet.* 6:1177-83, 1997) with regard to the menin cDNA and its translation product, *i.e.*, menin protein. The menin sequences of Chandrasekharappa *et al.* and Lemmens *et al.* are identical (*see,* the passage from the Online Mendelian Inheritance in Man, provided in Appendix B). Thus, there is a nexus between the sequences of the instant application and those referred to by Wautot *et al.* The Examiner has provided no evidence or reasoning as to why one of skill in the art would believe that the human menin sequences detected by Wautot *et al.* are somehow different from the sequences of Guru *et al.*, Chandrasekharappa, and Lemmens *et al.* Thus, the rejection is again improper.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

New grounds of rejection

Claims 2-4, and 32--rejection under 35 § U.S.C. § 112, first paragraph-written description

The Examiner alleges that claims 2-4 and 32 are not described such that one of skill in the art would recognize that at the time the application was filed, Applicants had possession of the claimed invention. The Examiner alleges that the specification "only" sets forth the genomic sequence of the 9.2 kb menin genomic clone (SEQ ID NO:3) and that this provides an inadequate basis for claiming a sequence that comprises noncoding regions, introns, or a sequence that comprises SEQ ID NO:3. To the extent that the rejection applies to the amended claims, Applicants traverse.

The Examiner cites *The Regents of the University of California v. Eli Lilly* ("*Lilly*") and *Vas-Cath Inc. v. Mahurkar* to support the argument that Applicants must describe the invention such that one of skill in the art recognizes that the inventors had possession at the time of filing the application, and that such a description can be achieve by providing structural properties of the claimed invention. Applicants have done precisely that. The claims recite SEQ ID NO:3. The open "comprising" language may indeed allow a practitioner to add one or more nucleotides to this sequence, but all of the sequences encompassed by the claim include the nucleotide sequence of SEQ ID NO:3. Thus, the claims recite a structural hallmark to identify the sequences encompassed by the claim. The MPEP (§2163(II)(3)(a)), quoting *Lilly*, states that "[I]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompasses. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." Here, one of skill can identify the species encompassed by the claims. This meets the requirements explicitly stated in *Lilly*. The Examiner's insistence that Applicants must provide additional sequence from the chromosome region that comprises the 9.2 kb menin gene in order to provide proper written description is therefore not properly founded in the case law.

Further, the application teaches that *MEN1* genes can be included in any number of expression vectors for the production of recombinant menin and reconstitution of menin activity (*see, e.g.*, page 29). Thus, Applicants have, in addition to providing a structural feature

of the claimed sequences, provided a listing of various species encompassed by the claimed genus. This further comports with the written description requirement set forth in *Lilly*.

Last, Applicants note that "isolated" as defined in the context of this invention, refers to a gene that is separated from open reading frames which flank the gene and encode a protein other than the *MEN1* gene product (*see, e.g.*, page 10, lines 9-10). Thus, the Examiner's concerns do not appear to relate to an "isolated" nucleic acid as set forth in the claims directed to SEQ ID NO:3.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Claims 2-4, 32--rejection under 35 U.S.C. § 112, first paragraph-enablement

Claims 2-4 and 32 are rejected as allegedly not enabled for a polynuclotide comprising SEQ ID NO:3. The Examiner contends that a polynucleotide comprising SEQ ID NO:3 encompasses polynucleotides comprising additional genes and that one of skill would not know how to use these other genes. To the extent that the rejection applies to the amended claims, Applicants traverse.

As noted above, the claims at issue relate to polynucleotide that comprise SEQ ID NO:3. The Examiner contends that the application has not taught those in the art how to use the claimed invention. However, the application contains extensive direction for using the claimed sequences. For example, the application teaches how to use the sequence in expression vectors (*see, e.g.*, the section begin on page 24). The application teaches how to use the sequences as probes to evaluate *MEN1* DNA in a nucleic acid sample (*see, e.g.*, page 33, lines 23-30). Thus, the application provides proper guidance for the use of the claimed sequences. The fact that one or more nucleotides may be added to SEQ ID NO:3 does not negate the ability of a practitioner to make and use the claimed sequences. Accordingly, the claimed are adequately enabled by the specification. Applicants therefore request withdrawal of the rejection.

Rejection of claims 30, 32, 33, 36, or 37--enablement

Claims 30, 32, 33, 36, or 37 were rejected as allegedly not enabled because they read on *in vivo* use. Applicants believe that the amendment to claim 30 obviates this rejection and therefore requests its withdrawal.

Rejection of claims 1-3, 5, 6, 30, 32, 33, 36, 37--written description

Claims 1-3, 5, 6, 30, 32, 33, 36, and 37 are rejected as allegedly lacking adequate written description. The Examiner alleges that sequences that have at least 95% identity to SEQ ID NO:2 are not adequately described in the specification. Applicants respectfully traverse. As the examiner knows, written description of a genus can be achieved by a precise definition, such as by structure, formula or chemical names. In *Lilly*, a generic statement such as a vertebrate insulin cDNA or mammalian insulin cDNA without more is not an adequate written description (emphasis added). Here, the claims do not merely recite a generic statement, they recite a structural feature: at least 95% identity to the reference sequence, SEQ ID NO:2. As in *Enzo*, quoted by the Examiner, the specification provides a structural hallmark (a reference sequence). Applicants additionally provide guidance as to substitutions and regions of the protein that when mutated, lead to loss of function (*see, e.g.,* the mutations identified in patients with multiple endocrine neoplasia type 1 that are described in Example 1, Figure 3, and Figure 4). Applicants claim sequences encoding a polypeptide having a high degree, 95%, identity to SEQ ID NO:2. In view of the reference sequence described in the specification, and further in view of the description of regions of the protein that are sensitive to mutation, Applicants have provided sufficient identifying characteristics of the claimed invention. Applicants therefore request withdrawal of the rejection.

Rejection of claims 19-24 and 26-written description

The Examiner alleges that the claims drawn to methods of detecting the presence or absence of a mutation in a human MEN1 gene comprising a nucleotide sequence that encodes a human menin as set forth in SEQ ID NO:2, or the presence or absence of the *MEN1* gene are not adequately described in the specification. In particular, the Examiner argues that the

specification does not describe a nucleotide sequence encoding human menin of SEQ ID NO:2 other than the cDNA and genomic sequences set forth in SEQ ID NO:3 and therefore fails to meet the written description requirement as set forth in *Lilly* or *Enzo*. Applicants respectfully traverse. As noted above, the claims recite a structural hallmark, the reference sequence, which provides identifying characteristics of the genus of nucleic acids encoding SEQ ID NO:2. Moreover, the MPEP unequivocally states that "in the molecular biology arts, if an applicant discloses an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acid encoding a given amino acid sequence" (MPEP §2163 (II)(3)(a)(ii)). Thus, human menin polymorphisms and allelic variants that encode SEQ ID NO:2 are acknowledged in the MPEP to be readily recognizable by those in the art. Applicants have thus satisfied the written description requirement. Withdrawal of the rejection is therefore requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 32 is rejected as indefinite for the lack of antecedent basis for the phrase exogenous nucleic acid". Applicants believe that the amendment to claim 32 obviates this rejection and therefore request its withdrawal.

Rejection under 35 U.S.C. § 102(b)

Claims 1-6, 30, 32, 33, 36, and 37 are rejected as anticipated by US Patent No. 4,594,318 (the '318 patent) as evidenced by Guru *et al* (*Mammalian Genome*, 1999). The rejection alleges that the '318 patent teaches isolated human chromosome 11 that comprises SEQ ID NO:3. Applicants traverse.

The '318 patent discloses extraction of genomic DNA from a hybrid cell line containing a deletion mutant of chromosome 11. The only human chromosome is the mutant chromosome 11; however, chromosomes from the other species, hamster, are present. Thus, the "isolated" genomic DNA in fact comprises many, many chromosomal sequences. Accordingly,

the isolated genomic DNA from the hybrid cell line does not constitute an isolated nucleic acid as claimed in the instant application.

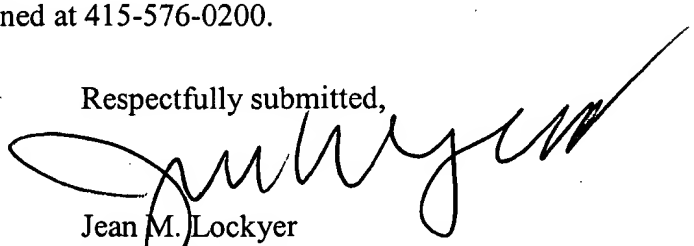
The '318 patent further discloses that the genomic DNA from the somatic cell hybrid was then cloned into a phage library. The Examiner appears to be concerned that the library would inherently have a clone that comprises a *MEN1* gene that encodes SEQ ID NO:2. However, there is no teaching that this genomic DNA library in fact contained a clone comprising any menin sequences. Moreoever, there is certainly no teaching that a fragment containing encoding a full-length human menin was present in a clone in this library. The MPEP§ 2131.01(III) explains that when a reference is silent about an asserted inherent characteristic, extrinsic evidence may be provided to fill in the gap. However, "[S]uch evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (emphasis added). The Examiner provides no such evidence. Accordingly, the rejection is improper. Applicants therefore request its withdrawal.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Jean M. Lockyer
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
JML:jml 60336060 v1


```
LOCUS       HSU93236                2772 bp    mRNA    linear   PRI 19-APR-1997
DEFINITION  Human menin (MEN1) mRNA, complete cds.
ACCESSION   U93236
VERSION     U93236.1  GI:1945386
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 2772)
  AUTHORS   Chandrasekharappa,S.C., Guru,S.C., Manickam,P., Olufemi,S.-E.,
            Collins,F.S., Emmert-Buck,M.R., Debelenko,L.V., Zhuang,Z.,
            Lubensky,I.A., Liotta,L.A., Crabtree,J.S., Wang,Y., Roe,B.A.,
            Weisemann,J., Boguski,M.S., Agarwal,S.K., Kester,M., Kim,Y.S.,
            Heppner,C., Dong,Q., Spiegel,A.M., Burns,A.L. and Marx,S.J.
  TITLE     Positional cloning of the gene for multiple endocrine
            neoplasia-type 1
  JOURNAL   Science 276 (5311), 404-407 (1997)
  MEDLINE   97258940
   PUBMED   9103196
REFERENCE   2  (bases 1 to 2772)
  AUTHORS   Collins,F.S.
  TITLE     Direct Submission
  JOURNAL   Submitted (13-MAR-1997) National Human Genome Research Institute,
            Bldg 38A, Room 605, National Institutes of Health, Bethesda, MD
            20892, USA
FEATURES             Location/Qualifiers
     source          1..2772
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="11"
                     /map="11q13"
     gene            1..2772
                     /gene="MEN1"
     exon            1..87
                     /gene="MEN1"
                     /number=1
     exon            88..555
                     /gene="MEN1"
                     /number=2
     CDS             111..1943
                     /gene="MEN1"
                     /codon_start=1
                     /product="menin"
                     /protein_id="AAC51228.1"
                     /db_xref="GI:1945387"
                     /translation="MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFV
                     EHFLAVNRVIPTNVPELTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVD
```

```
                     LSLYPREGGVSSRELVKKVSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFA
                     VVGACQALGLRDVHLALSEDHAWVVFGPNGEQTAEVTWHGKGNEDRRGQTVNAGVAER
                     SWLYLKGSYMRCDRKMEVAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLERY
                     PMALGNLADLEELEPTPGRPDPLTLYHKGIASAKTYYRDEHIYPYMYLAGYHCRNRNV
                     REALQAWADTATVIQDYNYCREDEEIYKEFFEVANDVIPNLLKEAASLLEAGEERPGE
                     QSQGTQSQGSALQDPECFAHLLRFYDGICKWEEGSPTPVLHVGWATFLVQSLGRFEGQ
                     VRQKVRIVSREAEAAEAEEPWGEEAREGRRRGPRRESKPEEPPPPKKPALDKGLGTGQ
                     GAVSGPPRKPPGTVAGTARGPEGGSTAQVPAPAASPPPEGPVLTFQSEKMKGMKELLV
                     ATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTLSFLKRQRKGL"
variation            175
                     /gene="MEN1"
                     /standard_name="L22R"
                     /note="Lys22Arg"
                     /replace="g"
variation            357..360
                     /gene="MEN1"
                     /standard_name="357del4"
                     /note="4 bp deletion in kindred 0176"
                     /replace=""
variation            416
                     /gene="MEN1"
                     /standard_name="416delC"
                     /note="1 bp deletion"
                     /replace=""
variation            464..466
                     /gene="MEN1"
                     /standard_name="K119del"
                     /note="3 bp deletion"
                     /replace=""
variation            512
                     /gene="MEN1"
                     /standard_name="512delC"
                     /note="1 bp deletion"
                     /replace=""
exon                 556..764
                     /gene="MEN1"
                     /number=3
variation            704
                     /gene="MEN1"
                     /standard_name="W198X"
                     /note="Trp198stop"
                     /replace="a"
variation            735..738
                     /gene="MEN1"
                     /standard_name="735del4"
                     /note="4 bp deletion"
                     /replace=""
exon                 765..893
                     /gene="MEN1"
                     /number=4
exon                 894..934
                     /gene="MEN1"
                     /number=5
exon                 935..1022
                     /gene="MEN1"
                     /number=6
exon                 1023..1159
                     /gene="MEN1"
                     /number=7
variation            1132
```

```
                     /gene="MEN1"
                     /standard_name="1132delG"
                     /note="1 bp deletion"
                     /replace=""
     exon            1160..1295
                     /gene="MEN1"
                     /number=8
     variation       1197..1199
                     /gene="MEN1"
                     /standard_name="E363del"
                     /note="3 bp deletion"
                     /replace=""
     exon            1296..1460
                     /gene="MEN1"
                     /number=9
     variation       1416
                     /gene="MEN1"
                     /standard_name="W436R"
                     /note="Trp436Arg"
                     /replace="c"
     variation       1417
                     /gene="MEN1"
                     /standard_name="W436X"
                     /note="Trp436stop"
                     /replace="a"
     exon            1461..2772
                     /gene="MEN1"
                     /number=10
     variation       1689
                     /gene="MEN1"
                     /standard_name="R527X"
                     /note="Arg527stop"
                     /replace="t"
ORIGIN
        1 ggtgtccgga gccgcggacc tagagatccc agaagccaca gcgcagcggc ccggcccgcc
       61 actatttcca ggctctgcgg ggcaggggcc gccgcccacc gcccgccgcc atggggctga
      121 aggccgccca gaagacgctg ttcccgctgc gctccatcga cgacgtggtg cgcctgtttg
      181 ctgccgagct gggccgagag gagccggacc tggtgctcct ttccttggtg ctgggcttcg
      241 tggagcattt tctggctgtc aaccgcgtca tccctaccaa cgttcccgag ctcaccttcc
      301 agcccagccc cgcccccgac ccgcctggcg gcctcaccta ctttcccgtg gccgacctgt
      361 ctatcatcgc cgccctctat gcccgcttca ccgcccagat ccgaggcgcc gtcgacctgt
      421 ccctctatcc tcgagaaggg ggtgtctcca gccgtgagct ggtgaagaag gtctccgatg
      481 tcatatggaa cagcctcagc cgctcctact tcaaggatcg ggcccacatc cagtccctct
      541 tcagcttcat cacaggcacc aaattggaca gctccggtgt ggcctttgct gtggttgggg
      601 cctgccaggc cctgggtctc cgggatgtcc acctcgccct gtctgaggat catgcctggg
      661 tagtgtttgg gcccaatggg gagcagacag ctgaggtcac ctggcacggc aagggcaacg
      721 aggaccgcag gggccagaca gtcaatgccg gtgtggctga gcggagctgg ctgtacctga
      781 aaggatcata catgcgctgt gaccgcaaga tggaggtggc gttcatggtg tgtgccatca
      841 acccttccat tgacctgcac accgactcgc tggagcttct gcagctgcag cagaagctgc
      901 tctggctgct ctatgacctg ggacatctgg aaaggtaccc catggcctta gggaacctgg
      961 cagatctaga ggagctggag cccacccctg gccggccaga cccactcacc ctctaccaca
     1021 agggcattgc ctcagccaag acctactatc gggatgaaca catctacccc tacatgtacc
     1081 tggctggcta ccactgtcgc aaccgcaatg tgcgggaagc cctgcaggcc tgggcggaca
     1141 cggccactgt catccaggac tacaactact gccgggaaga cgaggagatc tacaaggagt
     1201 tctttgaagt agccaatgat gtcatcccca acctgctgaa ggaggcagcc agcttgctgg
     1261 aggcgggcga ggagcggccg ggggagcaaa gccagggcac ccagagccaa ggttccgccc
     1321 tccaggaccc tgagtgcttc gcccacctgc tgcgattcta cgacggcatc tgcaaatggg
     1381 aggagggcag tcccacgcct gtgctgcacg tgggctgggc caccttttctt gtgcagtccc
     1441 taggccgttt tgagggacag gtgcggcaga aggtgcgcat agtgagccga gaggccgagg
     1501 cggccgaggc cgaggagccg tggggcgagg aagcccggga aggccggcgg cggggcccac
```

```
1561 ggcgggagtc caagccagag gagcccccgc cgcccaagaa gccagcactg gacaagggcc
1621 tgggcaccgg ccagggtgca gtgtcaggac ccccccggaa gcctcctggg actgtcgctg
1681 gcacagcccg aggccctgaa ggtggcagca cggctcaggt gccagcaccc gcagcatcac
1741 caccgccgga gggtccagtg ctcactttcc agagtgagaa gatgaagggc atgaaggagc
1801 tgctggtggc caccaagatc aactcgagcg ccatcaagct gcaactcacg gcacagtcgc
1861 aagtgcagat gaagaagcag aaagtgtcca cccctagtga ctacactctg tctttcctca
1921 agcggcagcg caaaggcctc tgaactactg gggacttcgg accgcttgtg gggacccagg
1981 ctccgcctta gtcccccaac tctgagccca tgttctgccc ccagcccaaa ggggacaggc
2041 ctcacctcta cccaaaccct aggttcccgg tcccgagtac agtctgtatc aaacccacga
2101 ttttctccag ctcagaaccc agggctctgc cccagtcgtt agaatatagg tctcttctcc
2161 cagaatccca gccggccaat ggaaacctca cgctgggtcc taattaccag tctttaaagg
2221 cccagccccc agaaacccaa gctcctcctc ggaaccgctc acctagagcc agaccaacgt
2281 tactcagggc tcctcccagc ttgtaggagc tgaggtttca cccttaaccc aagggagcac
2341 aggtcccacc tccagcccgg ggagcctagg accactcagc ccctaggagt atatttccgc
2401 acttcagaat tccatatctt gcgaatccaa gctccctgcc ccaaataact tcagtcctgc
2461 ttccagaatt tggaaatcct agtttcctct ccttcgtatc ccgagtctgg gacacaaaac
2521 tccgccccca gcctatgagc atcctgagcc ccgccctctt cctgacgaaa ctggccccgg
2581 atcagagcag gacctccctt ccgaccctct gggaacctcc cagaggtcca gcccatctcg
2641 gagcatcccg gaggaaatct gcagaggggt taggagtggg tgacaagagc ctgatctctt
2701 cctgttttgt acatagattt atttttcagt tccaagaaag atgaatacat tttgttaaaa
2761 aaaaaaaaaa aa
//
```

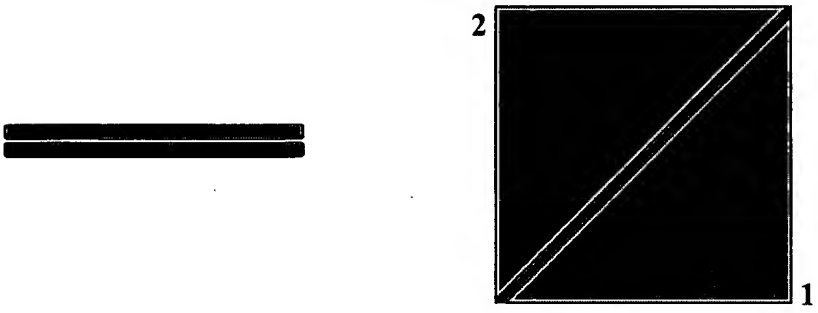
Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.10 [Oct-19-2004]

Match: 1 Mismatch: -2 gap open: 5 gap extension: 2
x_dropoff: 50 expect: 10.000 wordsize: 11 Filter ☐ Align

Sequence 1 lcl|seq_1 **Length** 2772 (1 .. 2772)
Sequence 2 lcl|seq_2 **Length** 2772 (1 .. 2772)



NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

NOTE:If protein translation is reversed, please repeat the search with reverse strand of the query sequence

```
Score = 5330 bits (2772), Expect = 0.0
Identities = 2772/2772 (100%)
 Strand = Plus / Plus
```

```
Query: 1    ggtgtccggagccgcggacctagagatcccagaagccacagcgcagcggcccggcccgcc 60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1    ggtgtccggagccgcggacctagagatcccagaagccacagcgcagcggcccggcccgcc 60

Query: 61   actatttccaggctctgcggggcaggggccgccgcccaccgcccgccgccatggggctga 120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 61   actatttccaggctctgcggggcaggggccgccgcccaccgcccgccgccatggggctga 120

Query: 121  aggccgcccagaagacgctgttcccgctgcgctccatcgacgacgtggtgcgcctgtttg 180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 121  aggccgcccagaagacgctgttcccgctgcgctccatcgacgacgtggtgcgcctgtttg 180

Query: 181  ctgccgagctgggccgagaggagccggacctggtgctcctttccttggtgctgggcttcg 240
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 181  ctgccgagctgggccgagaggagccggacctggtgctcctttccttggtgctgggcttcg 240
```

```
Query: 241  tggagcattttctggctgtcaaccgcgtcatccctaccaacgttcccgagctcaccttcc 300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 241  tggagcattttctggctgtcaaccgcgtcatccctaccaacgttcccgagctcaccttcc 300

Query: 301  agcccagccccgcccccgacccgcctggcggcctcacctactttcccgtggccgacctgt 360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 301  agcccagccccgcccccgacccgcctggcggcctcacctactttcccgtggccgacctgt 360

Query: 361  ctatcatcgccgccctctatgcccgcttcaccgcccagatccgaggcgccgtcgacctgt 420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 361  ctatcatcgccgccctctatgcccgcttcaccgcccagatccgaggcgccgtcgacctgt 420

Query: 421  ccctctatcctcgagaaggggtgtctccagccgtgagctggtgaagaaggtctccgatg 480
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 421  ccctctatcctcgagaaggggtgtctccagccgtgagctggtgaagaaggtctccgatg 480

Query: 481  tcatatggaacagcctcagccgctcctacttcaaggatcgggcccacatccagtccctct 540
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 481  tcatatggaacagcctcagccgctcctacttcaaggatcgggcccacatccagtccctct 540

Query: 541  tcagcttcatcacaggcaccaaattggacagctccggtgtggcctttgctgtggttgggg 600
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 541  tcagcttcatcacaggcaccaaattggacagctccggtgtggcctttgctgtggttgggg 600

Query: 601  cctgccaggccctgggtctccgggatgtccacctcgccctgtctgaggatcatgcctggg 660
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 601  cctgccaggccctgggtctccgggatgtccacctcgccctgtctgaggatcatgcctggg 660

Query: 661  tagtgtttgggcccaatggggagcagacagctgaggtcacctggcacggcaagggcaacg 720
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 661  tagtgtttgggcccaatggggagcagacagctgaggtcacctggcacggcaagggcaacg 720

Query: 721  aggaccgcaggggccagacagtcaatgccggtgtggctgagcggagctggctgtacctga 780
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 721  aggaccgcaggggccagacagtcaatgccggtgtggctgagcggagctggctgtacctga 780

Query: 781  aaggatcatacatgcgctgtgaccgcaagatggaggtggcgttcatggtgtgtgccatca 840
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 781  aaggatcatacatgcgctgtgaccgcaagatggaggtggcgttcatggtgtgtgccatca 840

Query: 841  acccttccattgacctgcacaccgactcgctggagcttctgcagctgcagcagaagctgc 900
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 841  acccttccattgacctgcacaccgactcgctggagcttctgcagctgcagcagaagctgc 900

Query: 901  tctggctgctctatgacctgggacatctggaaaggtaccccatggccttagggaacctgg 960
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 901  tctggctgctctatgacctgggacatctggaaaggtaccccatggccttagggaacctgg 960
```

```
Query: 961  cagatctagaggagctggagcccacccctggccggccagacccactcaccctctaccaca 1020
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 961  cagatctagaggagctggagcccacccctggccggccagacccactcaccctctaccaca 1020

Query: 1021 agggcattgcctcagccaagacctactatcgggatgaacacatctacccctacatgtacc 1080
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1021 agggcattgcctcagccaagacctactatcgggatgaacacatctacccctacatgtacc 1080

Query: 1081 tggctggctaccactgtcgcaaccgcaatgtgcgggaagccctgcaggcctgggcggaca 1140
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1081 tggctggctaccactgtcgcaaccgcaatgtgcgggaagccctgcaggcctgggcggaca 1140

Query: 1141 cggccactgtcatccaggactacaactactgccgggaagacgaggagatctacaaggagt 1200
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1141 cggccactgtcatccaggactacaactactgccgggaagacgaggagatctacaaggagt 1200

Query: 1201 tctttgaagtagccaatgatgtcatccccaacctgctgaaggaggcagccagcttgctgg 1260
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1201 tctttgaagtagccaatgatgtcatccccaacctgctgaaggaggcagccagcttgctgg 1260

Query: 1261 aggcgggcgaggagcggccgggggagcaaagccagggcacccagagccaaggttccgccc 1320
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1261 aggcgggcgaggagcggccgggggagcaaagccagggcacccagagccaaggttccgccc 1320

Query: 1321 tccaggaccctgagtgcttcgcccacctgctgcgattctacgacggcatctgcaaatggg 1380
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1321 tccaggaccctgagtgcttcgcccacctgctgcgattctacgacggcatctgcaaatggg 1380

Query: 1381 aggagggcagtcccacgcctgtgctgcacgtgggctgggccacctttcttgtgcagtccc 1440
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1381 aggagggcagtcccacgcctgtgctgcacgtgggctgggccacctttcttgtgcagtccc 1440

Query: 1441 taggccgttttgagggacaggtgcggcagaaggtgcgcatagtgagccgagaggccgagg 1500
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1441 taggccgttttgagggacaggtgcggcagaaggtgcgcatagtgagccgagaggccgagg 1500

Query: 1501 cggccgaggccgaggagccgtggggcgaggaagcccgggaaggccggcggcggggcccac 1560
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1501 cggccgaggccgaggagccgtggggcgaggaagcccgggaaggccggcggcggggcccac 1560

Query: 1561 ggcgggagtccaagccagaggagcccccgccgcccaagaagccagcactggacaagggcc 1620
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1561 ggcgggagtccaagccagaggagcccccgccgcccaagaagccagcactggacaagggcc 1620

Query: 1621 tgggcaccggccagggtgcagtgtcaggacccccccggaagcctcctgggactgtcgctg 1680
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1621 tgggcaccggccagggtgcagtgtcaggacccccccggaagcctcctgggactgtcgctg 1680
```

```
Query: 1681 gcacagcccgaggccctgaaggtggcagcacggctcaggtgccagcacccgcagcatcac 1740
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1681 gcacagcccgaggccctgaaggtggcagcacggctcaggtgccagcacccgcagcatcac 1740

Query: 1741 caccgccggagggtccagtgctcactttccagagtgagaagatgaagggcatgaaggagc 1800
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1741 caccgccggagggtccagtgctcactttccagagtgagaagatgaagggcatgaaggagc 1800

Query: 1801 tgctggtggccaccaagatcaactcgagcgccatcaagctgcaactcacggcacagtcgc 1860
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1801 tgctggtggccaccaagatcaactcgagcgccatcaagctgcaactcacggcacagtcgc 1860

Query: 1861 aagtgcagatgaagaagcagaaagtgtccacccctagtgactacactctgtctttcctca 1920
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1861 aagtgcagatgaagaagcagaaagtgtccacccctagtgactacactctgtctttcctca 1920

Query: 1921 agcggcagcgcaaaggcctctgaactactggggacttcggaccgcttgtggggacccagg 1980
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1921 agcggcagcgcaaaggcctctgaactactggggacttcggaccgcttgtggggacccagg 1980

Query: 1981 ctccgccttagtcccccaactctgagcccatgttctgcccccagcccaaaggggacaggc 2040
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 1981 ctccgccttagtcccccaactctgagcccatgttctgcccccagcccaaaggggacaggc 2040

Query: 2041 ctcacctctacccaaaccctaggttcccggtcccgagtacagtctgtatcaaacccacga 2100
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2041 ctcacctctacccaaaccctaggttcccggtcccgagtacagtctgtatcaaacccacga 2100

Query: 2101 ttttctccagctcagaacccagggctctgccccagtcgttagaatataggtctcttctcc 2160
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2101 ttttctccagctcagaacccagggctctgccccagtcgttagaatataggtctcttctcc 2160

Query: 2161 cagaatcccagccggccaatggaaacctcacgctgggtcctaattaccagtctttaaagg 2220
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2161 cagaatcccagccggccaatggaaacctcacgctgggtcctaattaccagtctttaaagg 2220

Query: 2221 cccagcccctagaaacccaagctcctcctcggaaccgctcacctagagccagaccaacgt 2280
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2221 cccagcccctagaaacccaagctcctcctcggaaccgctcacctagagccagaccaacgt 2280

Query: 2281 tactcagggctcctcccagcttgtaggagctgaggtttcacccttaacccaagggagcac 2340
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2281 tactcagggctcctcccagcttgtaggagctgaggtttcacccttaacccaagggagcac 2340

Query: 2341 aggtcccacctccagcccggggagcctaggaccactcagcccctaggagtatatttccgc 2400
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2341 aggtcccacctccagcccggggagcctaggaccactcagcccctaggagtatatttccgc 2400
```

```
Query: 2401 acttcagaattccatatcttgcgaatccaagctccctgccccaaataacttcagtcctgc 2460
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2401 acttcagaattccatatcttgcgaatccaagctccctgccccaaataacttcagtcctgc 2460


Query: 2461 ttccagaatttggaaatcctagtttcctctccttcgtatcccgagtctgggacacaaaac 2520
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2461 ttccagaatttggaaatcctagtttcctctccttcgtatcccgagtctgggacacaaaac 2520


Query: 2521 tccgcccccagcctatgagcatcctgagccccgccctcttcctgacgaaactggccccgg 2580
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2521 tccgcccccagcctatgagcatcctgagccccgccctcttcctgacgaaactggccccgg 2580


Query: 2581 atcagagcaggacctcccttccgaccctctgggaacctcccagaggtccagcccatctcg 2640
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2581 atcagagcaggacctcccttccgaccctctgggaacctcccagaggtccagcccatctcg 2640


Query: 2641 gagcatcccggaggaaatctgcagaggggttaggagtgggtgacaagagcctgatctctt 2700
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2641 gagcatcccggaggaaatctgcagaggggttaggagtgggtgacaagagcctgatctctt 2700


Query: 2701 cctgttttgtacatagatttatttttcagttccaagaaagatgaatacattttgttaaaa 2760
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 2701 cctgttttgtacatagatttatttttcagttccaagaaagatgaatacattttgttaaaa 2760


Query: 2761 aaaaaaaaaaaa 2772
           ||||||||||||
Sbjct: 2761 aaaaaaaaaaaa 2772

CPU time:     0.02 user secs.       0.02 sys. secs          0.04 total secs.

Lambda     K      H
    1.33    0.621     1.12

Gapped
Lambda     K      H
    1.33    0.621     1.12


Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 857
Number of extensions: 16
Number of successful extensions: 3
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Number of extra gapped extensions for HSPs above 10.0: 0
Length of query: 2772
Length of database: 12,276,950,563
Length adjustment: 27
Effective length of query: 2745
Effective length of database: 12,276,950,536
```

```
Effective search space: 33700229221320
Effective search space used: 33700229221320
Neighboring words threshold: 0
Window for multiple hits: 0
X1: 11 (21.1 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 12 (23.8 bits)
S2: 22 (43.0 bits)
```

AHNAK--ROM1--MDU1--CHRM1--COX8--EMK1--FKBP2--PLCB3--[PYGM, ZFM1]--FAU--CAPN1--[MLK3, RELA]--FOSL1--SEA--CFL1--tel. The location of MEN1 was narrowed to a 2-Mb region beginning centromeric to COX8 and extending to approximately CAPN1.

Guru et al. (1997) mapped and sequenced the MEN1 genomic region. They produced a precisely ordered map of 33 transcribed genes within this 2-Mb region.

The European Consortium on MEN1 (1997) constructed a 1.2-Mb sequence-ready contig encompassing the MEN1 region. They described 3 gene clusters, including the central cluster which contains the MEN1 gene.

By FISH, Guru et al. (1999) mapped the mouse Men1 gene to chromosome 19 in a region showing homology of synteny to human chromosome 11q13.

MOLECULAR GENETICS

Chandrasekharappa et al. (1997) identified several MEN1 candidate genes in a previously identified minimal interval on 11q13. One of the genes contained 12 different frameshift, nonsense, missense, and in-frame deletion mutations in 14 probands from 15 families (e.g., 131100.0001). The MEN1 gene contains 10 exons and encodes a ubiquitously expressed 2.8-kb transcript. The predicted 610-amino acid protein product, termed menin by them, exhibited no apparent similarities to any previously known proteins. They commented that the identification of the MEN1 gene should enable improved understanding of the mechanism of endocrine tumorigenesis and should facilitate early diagnosis.

To identify additional candidate genes in the segment of less than 300 kb where the MEN1 locus is situated, Lemmens et al. (1997) used a BAC to isolate cDNAs from a bovine parathyroid cDNA library by direct selection. One of the novel genes that they identified, called SCG2 (for 'suppressor candidate gene 2') by them, proved to be identical to the MEN1 gene reported by Chandrasekharappa et al. (1997). The SCG2 transcript was 2.9 kb in all tissues with an additional 4.2 kb transcript also being present in the pancreas and thymus. A human SCG2 cDNA clone, covering 2.3 kb at the 3-prime end of the gene, was isolated by hybridization screening. Northern blot analysis with this human sequence gave results identical to those from the bovine sequence. Mutational analysis of human SCG2 in 10 unrelated MEN1 families identified 1 polymorphism and 9 different heterozygous mutations (1 missense, 4 nonsense, 1 insertional, and 3 deletional frameshifts) that segregated with the disease, hence providing an independent confirmation for the identification of the MEN1 gene.

Agarwal et al. (1997) failed to find germline mutations of the MEN1 gene in 5 kindreds with familial hyperparathyroidism. Heppner et al. (1997) found somatic mutation of the MEN1 gene in 21% of parathyroid tumors not associated with MEN1, representing 54% of parathyroid tumors with 11q13 LOH. The authors suggested that parathyroid tumor formation in kindreds with somatic mutation of MEN1 may be initiated by germline mutation of an unidentified tumor suppressor gene or oncogene. The finding of somatic mutation (131100.0013) in a single tumor from a member of such a kindred indicated that somatic MEN1 gene mutation may also contribute to tumorigenesis in such individuals. Previous studies had found frequent 11q13 LOH in sporadic tumors as follows: gastrinoma (45%), insulinoma (19%), anterior pituitary gland tumors (3 to 30%), carcinoid tumors (78%), thyroid follicular tumors (15%), and aldosteronomas (36%). Heppner et al. (1997) suggested that many of these tumors likewise may have MEN1 somatic mutations. Whether somatic mutations of the MEN1 gene are confined to tumors of endocrine tissue or whether somatic mutation of the MEN1 gene is operative in tumor formation of nonendocrine tissues remained to be established.